UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/769,144	01/30/2004	Tibor Keler	CDJ-301RCE2	9318

959 7590 11/21/2008

LAHIVE & COCKFIELD, LLP
FLOOR 30, SUITE 3000
ONE POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER	
KIM, YUNSOO	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
11/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/769,144	KELER ET AL.	
	Examiner	Art Unit	
	YUNSOO KIM	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-36,39-44,47-52 and 55-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-36,39-44,47-52 and 55-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/3/08 has been entered.

2. Claims 33-36, 39-44, 47-52 and 55-59 are pending.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 33-36, 39-44, 47-52 and 55-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/85798 (IDS reference, of record) in view of U.S. Pat. No. 5,869,057 (IDS reference, of record) for the reasons set forth in the office action mailed on 4/10/08.

The '798 publication teaches a method of inducing an immune response by contacting antigen presenting cells (APC), particularly dendritic cells (DC), with a composition comprising a molecular conjugate (i.e. complex) of a human monoclonal antibody conjugated to a tumor antigen (p. 5-6, 54-55, claims, 33-42) in

conjunction with immunostimulatory cytokines such as GM-CSF, IL-2 and IFN-γ (see entire document, particularly the abstract, pages 2, 5-6, 8, 43, 53-57, and claims 33-42). The '798 publication also discloses a monoclonal antibody that binds to the macrophage mannose receptor present on DC, and that such antibodies are desirable for practicing the methods disclosed in the '798 publication (see particularly claims 5 and 34). The conjugates of the '798 publication are disclosed as being formed in various ways, including as fusion proteins produced recombinantly (see particularly pages 5, 44, 54, 55). The antibodies used in such conjugates are disclosed as being human, humanized, chimeric and antigen binding fragments such as Fab and scFv (see particularly pages 36 and 39). Notably, the '798 publication teaches the antibody comprising SEQ ID NOs:4 and 8 recited in the instant claims (see particularly Fig. 13, B11 V_L and B11 V_H proteins). Note that the recited SEQ ID NOs:4 and 8 encompass the CDRs identified as in SEQ ID NOs:13-18 in dependent claims 41-43. Moreover, the '798 publication teaches *in vivo and ex vivo* internalization of the antibody-antigen by APC which leads to the generation of immune responses mediated by MHC-I/II complexes including the elicitation of CD4+, CD8+ and cytotoxic T cells (see particularly pages 5-6, 26, 35, 36, 38-41, 56-58 and claims 5, 16, 23-27, 32, 38-42).

The disclosure of the '798 publication differs from the instant claimed invention in that it does not teach the use of βhCG as an antigen as is currently recited in claim 1 of the instant application.

The '057 patent teaches the use of βhCG as an antigen that is detectable on 74 different cancer cell lines (see entire document, particularly col. 3, lines 40-50, and col. 5, lines 32-60). The '057 patent further teaches that the βhCG is expressed and is detectable on the surface of tumor cells and could be used in immunization against βhCG and an antimetastasis treatment.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ βhCG as a tumor antigen as taught by the '057 patent in the molecular conjugate comprising a human monoclonal antibody that binds to dendritic cells and immunostimulatory cytokine taught by the '798 publication.

One of ordinary skill in the art would have been motivated to do so because of the well known characteristics of βhCG as a tumor antigen in treatment and its availability on many known tumor cells as taught by the '057 patent (col. 3, col. 5, in particular).

From the teachings of references, it would have been obvious to one of ordinary skill in the art to combine the teachings of the references and there would have been a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time of invention was made, as evidenced by references, especially in the absence of evidence to the contrary.

Applicants' arguments filed on 9/3/08 have been fully considered but they were not persuasive.

Applicants' traversal is based on the fact that the '057 patent fails to teach the claimed methods which employ a conjugate of βhCG and an antibody against MMR to form a molecular conjugate which directly targets the human MMR on APC and induces an immune response mediated by both CD4+ and CD8+ T cells.
Applicants further argued that the '057 patent requires addition of adjuvant for processing and presentation of T cell epitope by APC and this is done by microbial gene product. Applicants argued that the βhCG based vaccine requires an adjuvant and a carrier and cited Lund et al and Triozzi et al. references while the claimed method does not require such adjuvant. It is noted that Applicant fails to provide both references for consideration.

Contrary to Applicants' arguments, methods which employ a conjugate of antigen and an antibody against MMR to form a molecular conjugate which directly targets the human MMR on APC and induces an immune response mediated by both CD4+ and CD8+ T cells were taught by the '798 publication. The CTL response mediated by CD4+ and CD8+ T cells and MHC-I/II complexes are taught throughout the '798 publication and such immune response are achieved by the molecular conjugation of monoclonal antibody that binds to the macrophage mannose receptor on APC and a tumor antigen. Indeed, beginning on page 54, the '798 publication discloses:

> In another embodiment, the methods and compositions of the invention can be used to modulate an immune response in a subject towards an antigen. The human anti-dendritic cell antibodies of the invention can be used to target an antigen to a dendritic cell and thereby modulate antigen presentation and processing, such that an immune response to the antigen is induced. The antigen can be a tumor antigen, or an antigen from a pathogen, e.g., a microbial pathogen. The pathogen can be a virus (e.g., HIV), a bacterium, a fungus, or a parasite. The

> antigen can also be a component of an amyloid deposit in a patient, such as a patient suffering from Alzheimer's disease and the antigen is Aβ peptide.
>
> For example, a molecular complex comprising at least one binding specificity for a component on the surface of a dendritic cell linked to an antigen, wherein binding of the complex to the dendritic cell mediates internalization of the molecular complex, can be administered to a subject to induce or enhance an immune response against the antigen. The immune response generated against the antigen includes antibodies that bind to the antigen and T cells that bind to the antigen as a component of an MHC-I or MHC-II complex. Accordingly, the human anti-dendritic cell antibodies of the invention can also be used to mediate dendritic cell-targeted immunization of a subject. For example, a subject can be immunized with a molecular complex comprising at least one binding specificity for a component on the surface of a dendritic cell linked to an antigen, wherein binding of the complex to the dendritic cell mediates internalization of the molecular complex, and, for example, enhances processing and presentation of the antigen.

Thus, it is clear that the '798 publication discloses methods whereby an tumor antigen is targeted for efficient uptake and presentation on MHC class I and II molecules via conjugation of the tumor antigen to an dendritic-cell specific antibody.

The '057 patent is provided to show the motivation to select the βhCG as a tumor antigen because it is expressed and detectable on the surface of many tumor cells. The '057 patent further discloses that βhCG is to be used for immunization and as an antimetastasis treatment (col. 3, lines 40-50, col. 5, lines 32-60).

Therefore, a person of ordinary skill in the art would have been motivated to use βhCG as the tumor antigen in the methods of generating an anti-tumor antigen immune response that are disclosed in the '798 publication since the '057 patent discloses that βhCG is a tumor antigen that is to be used in vaccines to stimulate an immune response to the tumor antigen, and that βhCG is a particularly desirable tumor antigen to target because it is expressed on a wide variety of different tumors.

Applicants has argued on p. 7 of the response filed on 9/3/08 that the βhCG based vaccine of the '057 patent requires the adjuvant for processing and presentation of T cell epitopes by specialized APC and that therefore one of skilled in the art would not be motivated to link βhCG with an antibody.

This argument is not persuasive. First, the instant claim language does not preclude the presence of foreign T helper epitopes in the recited conjugate, and as such applicant is arguing limitations not claimed. Note that since the vaccine compositions of the '057 patent are useful because they induce an immune response, and because the '798 publication discloses methods by which immune responses are increased by specifically targeting antigens to the APC which are responsible for initiating the immune response, a person of ordinary skill in the art would be motivated to use the constructs of the '057 patent in the constructs of the '798 publication in order to induce a stronger immune response by virtue of increasing antigen presentation.

Second, the '057 patent discloses generically that βhCG is a tumor antigen. Tumor antigens are self antigens, and as such they all display some degree of "self-tolerance". Note that the '798 patent explicitly states that tumor antigens are to be used but does not require the presence of foreign T helper epitopes. Rather, it is the direct targeting of the antigen to dendritic cells with the optional addition of adjuvants such as cytokines that is responsible for the generation of anti-tumor antigen immune responses in the methods of the '798 publication. Note that the carrier and adjuvants that applicant argues are necessarily present in βhCG vaccines are present to ensure an adequate immune response to the antigen (i.e. βhCG), yet the methods disclosed by the '798 publication ensure efficient immune responses by targeting the tumor antigen to the antigen presenting cell. Thus the same effect can be achieved through different structural and functional mechanisms.

Given that the obviousness does not require absolute predictability but only the reasonable expectation (MPEP 2143.02) and one cannot show nonobviousness by attacking references individually (MPEP 2145), the claimed invention remains obvious.

5. The following new rejection is set forth herein.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 41-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that binds to the macrophage mannose receptor of antigen presenting cell (APC) wherein the antibody consists of variable heavy (VH) and variable light (VL) chain as in SEQ ID NO: 4 and 8, or comprises all 6 CDRs identified as in SEQ ID NOs: 13-18, does not reasonably provide enablement for any antibody comprising one specifically identified CDR from the VL and one specifically identified CDR from the VH chain as recited in claims 41-43.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The antibody recited in the claimed method is drawn to any antibody that binds to the macrophage mannose receptor on the APC and comprises any one CDR from each heavy and light variable region.

Even though it is known that the CDR3 is important, the conformations of other CDRs as well as framework residues influence binding. *MacCallum et al. J. Mol. Biol. (1996) 262, 732-745*, analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). *Pascalis et al. The Journal of Immunology (2002) 169, 3076-3084* demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

Given the established unpredictability of the art, the instant specification would require to show that one CDR from the variable heavy and the variable light domain is solely responsible for antigen binding and the instant specification would require to disclose that one CDR of variable light chain and heavy chain would be able to screen for entire antibodies just by defining one CDR. The methods rely on using an entire variable heavy or variable light and screen random complementary chains. *Chen et al.(J. Mol. Bio. (1999) 293, 865-881)* describe high affinity variant antibodies binding to VEGF wherein the results show

that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Thus, the art recognizes that a complete variable heavy chain or variable light chain is required to perform screening assay to identify antibodies that meet the structural and functional properties recited in the instant claims. However, the instant claims recite only one CDR from each variable domain and this level of structural information would not permit a skilled artisan to screen for antibodies to be used in the claimed methods.

To summarize, reasonable correlation must exist between the scope or the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breath of the claims, it would take undue trials and errors to practice the claimed invention.

8. No claims are allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yunsoo Kim whose telephone number is 571-272-3176. The examiner can normally be reached on M-F, 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Yunsoo Kim
Patent Examiner
Technology Center 1600
November 17, 2008

/Michael Szperka/
Primary Examiner, Art Unit 1644